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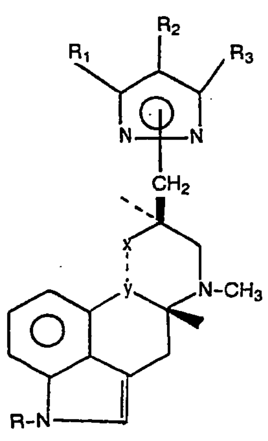
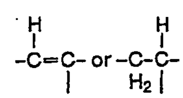
(54) **Pyrazole derivatives with an ergoline skeleton, a process for preparing them and pharmaceutical compositions containing these compounds.**

(57) The subject matter of the application are pyrazole derivatives with an ergoline skeleton of general formula




I,

wherein
x . . . y stands for a group of formula




,

R means a hydrogen atom or a methyl group,
$R_1$ represents a hydrogen atom or a $C_{1-4}$-alkyl, carbethoxy or pyridyl group and either
$R_2$ stands for a hydrogen atom or a $C_{1-4}$-alkyl, allyl, $C_{2-4}$-oxoalkyl, $C_{2-4}$-hydroxyalkyl or $C_{2-4}$-hydroxyiminoalkyl group and
$R_3$ means a hydrogen atom or a $C_{1-4}$-alkyl, hydroxy or pyridyl group or
$R_2$ and $R_3$ together stand for a group of general formula II of claim 1,
as well as their salts as well as a process for preparing them and pharmaceutical compositions containing these compounds.
The above compounds above all are potent $PGF_{2\alpha}$ receptor antagonists.

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The invention is concerned with novel pyrazole derivatives with an ergoline skeleton as well as with a process for preparing them and pharmaceutical compositions, particularly with antiprostaglandin ($PGF_{2\alpha}$ antagonist), antiserotonine, hypotensive, prolactine-level reducing and dopamine receptor agonist effects, containing these compounds.

The effect of compounds with an ergoline skeleton on the uterine musculature is known for a long time. The most potent uterotonic compounds, inducing uterine contraction, widely applied in therapy, belong to this group of substances (methylergometrin, ergometrin, ergotamine). Within the same family of compounds there are, however, also uterine relaxants (bromocryptine, dihydroergotamine, hydergine). Thus the ergoline skeleton undoubtedly has a specific affinity to the uterine musculature.

Exploiting this phenomenon it was the aim to prepare novel compounds with an ergoline skeleton which are competitive inhibitors of the receptor activity of the most potent endogeneous compound inducing uterine contraction, prostaglandin $F_{2alpha}$ ($PGF_{2alpha}$=9α,11α,15(S)--trihydroxy-5cis,13trans-prostadienoic acid). Such compounds are unknown yet, though they could be of major therapeutic importance in obstetrics, gynecology and neonatology (such as dysmenorrhea, anovulation, gestational toxicosis, habitual abortus, premature delivery and oc-

- 3 -

clusion of Botallo's duct), in conditions where there is a pathogenic overproduction of the highly active, endogenic uterotonic agent. Due to the pathophysiological effect of $PGF_{2alpha}$ these compounds could exhibit advantageous therapeutic activity in other conditions, too (such as bronchial asthma, disturbances in gastrointestinal motility, rheumatic conditions and anaphylaxis).

Pyrazole derivatives with an ergoline skeleton were first mentioned by A. Hofmann in Swiss Patent No. 392,531, but the (pyrazolylcarbonyl)-ergoline compound described by him was acid sensitive, and only the intermediary in the conversion of lysergic acid hydrazide to lysergic acid could be isolated. The inventors of US Patent 3,184,234 describe pyrazole-carboxamido-ergoline derivatives exhibiting antiulcer activity.

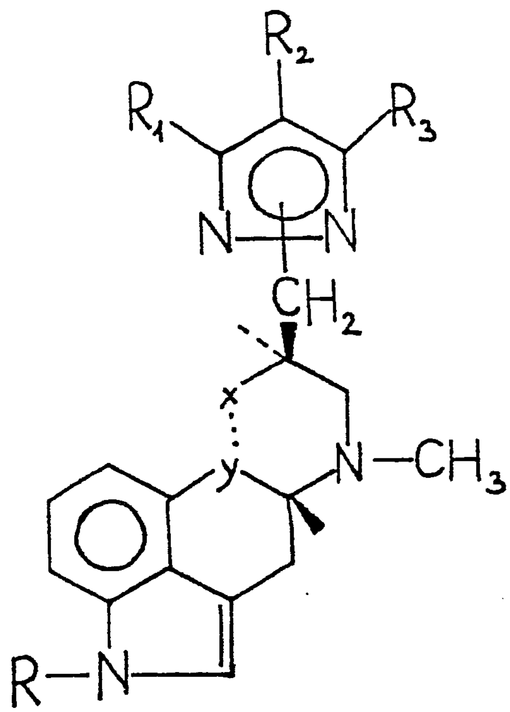
The problem underlying to the invention is to create novel pyrazole derivatives with an ergoline skeleton having superior pharmacological effects with a new mechanism of action, a process for preparing them and pharmaceutical compositions containing these compounds.

The above surprisingly has been attained by the invention.

The pyrazol-1-yl-methylen-ergoline derivatives of the invention are different from the former compounds both as regards biological and chemical properties, and

up till now were not reported in the literature.

The subject-matter of the invention are pyrazole derivatives with an ergoline skeleton of general formula



I ,

wherein

x...y stands for a group of formula

$$-\overset{H}{\underset{}{C}}=\underset{|}{C}- \quad \text{or} \quad -\underset{H_2}{C}-\overset{H}{\underset{|}{C}}- \quad ,$$

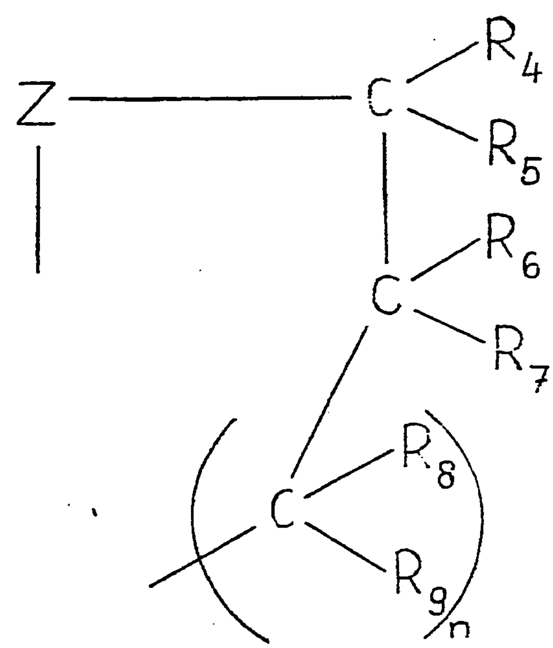
R means a hydrogen atom or a methyl group,

$R_1$ represents a hydrogen atom or a $C_{1-4}$-alkyl, carbethoxy or pyridyl group and either

$R_2$ stands for a hydrogen atom or a $C_{1-4}$-alkyl, allyl, $C_{2-4}$-oxoalkyl, $C_{2-4}$-hydroxyalkyl or $C_{2-4}$-hydroxyiminoalkyl group and

$R_3$ means a hydrogen atom or a $C_{1-4}$-alkyl, hydroxy or pyridyl group or

$R_2$ and $R_3$ together stand for a group of general formula




II ,

in which latter

Z stands for a methylene group, optionally substituted by one or two $C_{1-4}$-alkyl group(s), or a carbonyl, hydroxymethylene or hydroxyiminomethylene group,

$R_4$ , $R_5$ ,
$R_6$ , $R_7$ ,
$R_8$ and
$R_9$ , independently from each other, mean hydrogen atoms or $C_{1-4}$-alkyl groups and

n is 0 or 1,

as well as their pharmaceutically acceptable salts.

The circle in the above formula I symbolizes in the respective benzene ring three aromatic double bonds and in the pyrazole ring two conjugated double bonds none of them linking the two nitrogen atoms to each other. The bond starting from the methylene group and traversing the bond between the two nitrogen atoms of the pyrazole ring is to mean that it may be attached to each of these nitrogen atoms as alternatives.

Preferably the $C_{1-4}$-alkyl group(s) which may be represented by $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ and/or $R_9$ is or are such having 1 or 2, particularly 1, carbon atom(s).

It is also preferred that the $C_{2-4}$-oxoalkyl, $C_{2-4}$-hydroxyalkyl or $C_{2-4}$-hydroxyiminoalkyl group which may be represented by $R_2$ is such having 2 or 3, particularly 2, carbon atoms.

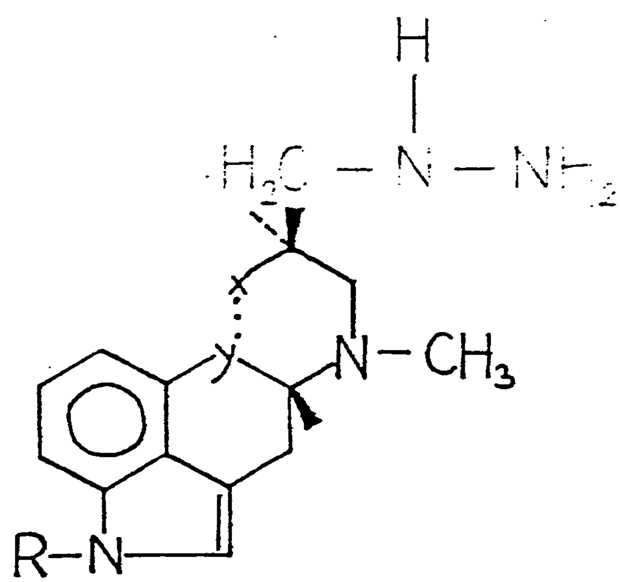
Furthermore it is preferred that the $C_{1-4}$-alkyl group(s) by which the methylene group for which Z may stand may be substituted is or are such having 1 or 2, particularly 1, carbon atom(s).

Moreover it is preferred that formula II has from 1 to 3 $C_{1-4}$-alkyl group(s) as [a] substituent(s).

Particularly preferably in case there is or are [a] $C_{1-4}$-alkyl group(s) on the cyclopentano or cyclohexano ring formed by formula II as [a] substituent(s) this is or these are, respectively, attached to the cyclopentano ring in its position 3 (or 5) and to the cyclohexano ring in its position(s) 3 (or 7) and/or 6 (or 4).

Particularly preferred compounds according to the invention are 8-β-{3(5)-methyl-cyclopentano[4,5(3,4)]pyrazol-1-yl-methylene}-6-methyl-ergol-9-ene and its hydrogen fumarate.

The subject matter of the invention is also a process for preparing the compounds according to the invention, which is characterized in that hydrazine compounds of general formula

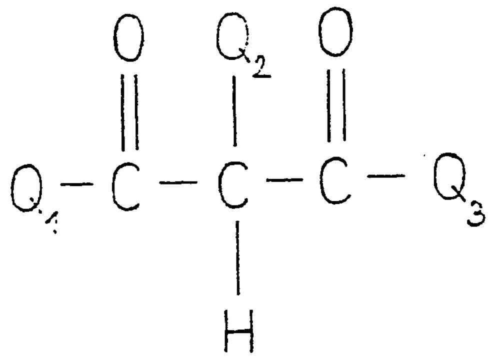


III ,

wherein x...y and R are as above defined,

are reacted

a) with β-diketones of general formula

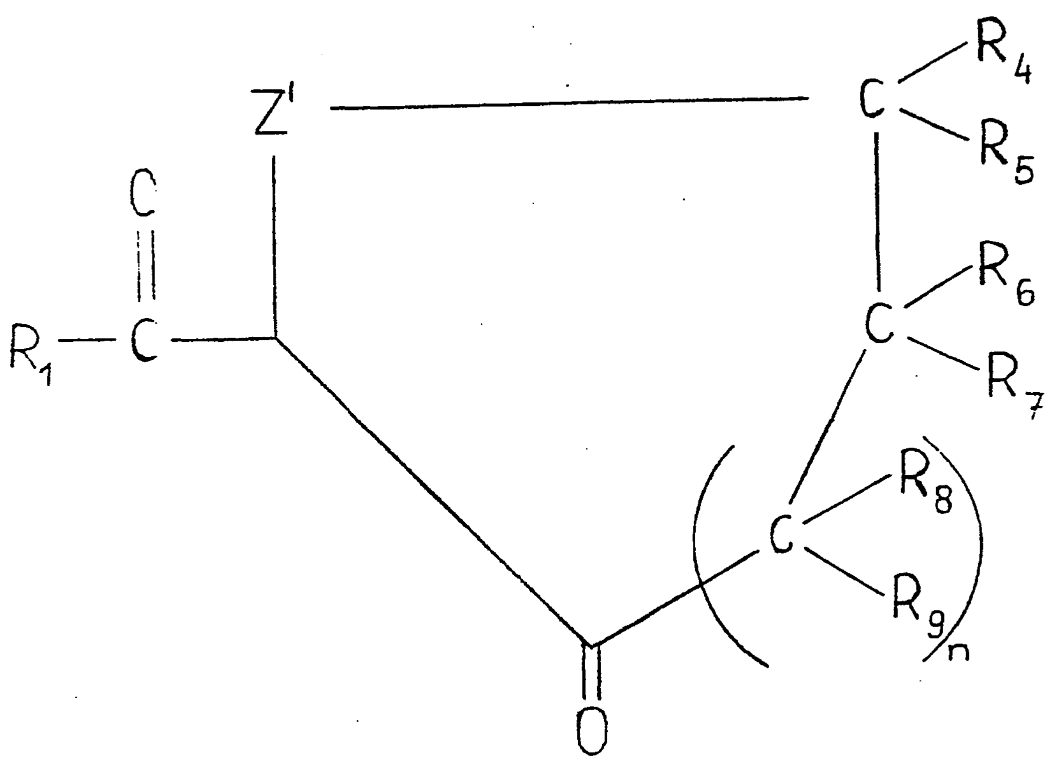


IV ,

wherein

| | |
|---|---|
| $Q_1$ and $Q_3$ , | independently from each other, stand for a $C_{1-4}$-alkyl, ethoxy, carbethoxy or pyridyl group and |
| $Q_2$ | represents a hydrogen atom or a $C_{1-4}$-alkyl, allyl or $C_{2-4}$--oxoalkyl group, or |

b) with cycloalkanones of general formula



V ,

wherein

$R_1$ , $R_4$ ,
$R_5$ , $R_6$ ,
$R_7$ , $R_8$ ,
$R_9$ and n are as above defined and

Z' stands for a methylene group, optionally substituted by one or two $C_{1-4}$-alkyl group(s), or for a carbonyl group,

whereafter, if desired, in a manner known per se the obtained pyrazole derivatives of general formula I in which x...y stands for a group of formula $-\overset{H}{\overset{|}{C}}=\underset{|}{C}-$ and/or $R_2$ represents a $C_{2-4}$-oxoalkyl group or Z represents a carbonyl group are reduced to those in which x...y stands for a group of formula $-\underset{H_2}{C}-\overset{H}{\overset{|}{\underset{|}{C}}}-$ and/or $R_2$ represents a $C_{2-4}$-hydroxyalkyl group or Z represents a hydroxymethylene group, respectively, or, if desired, the obtained pyrazole derivatives of general formula I in which $R_2$ represents a $C_{2-4}$-oxoalkyl group or Z represents a carbonyl group are converted into the corresponding pyrazole derivatives of general formula I being oximes in which $R_2$ represents a $C_{2-4}$-hydroxyiminoalkyl group or Z represents a hydroxyiminomethylene group, respectively, or , if desired, the obtained pyrazole derivatives of general formula I in which R stands for a hydrogen atom are methylated to the corresponding pyrazole derivatives of general formula I in which R stands for a methyl group and/or, if desired, the whatever obtained pyrazole derivatives of general formula I

are converted with acids into salts or, if desired, the whatever obtained salts of the pyrazole derivatives of general formula I are converted into the corresponding free bases of general formula I and/or into other salts.

At the use of asymmetric beta-diketones a mixture of isomers may be formed which can be separated into their components by column chromatography. In compounds where the position of the ergoline-methylene group on the pyrazole ring is not elucidated yet, the alternative structure is indicated, as usual, by a figure in brackets.

According to a preferred process a) or b) a diketone, either of general formula IV or V, is added at room temperature to a compound of general formula (III), dissolved in a lower alcohol, preferably in ethanol, tetrahydrofuran and/or acetonitrile, then the mixture is acidified to pH 3 or 4 by an inorganic or organic acid, preferably hydrochloric acid, and is stirred for 1 hour.

According to an other preferred process a) or b) compounds of general formula (III) and (IV) or (V) are dissolved in a lower alcohol, preferably methanol, whereafter boron trifluoride is added and the mixture is stirred for 1 hour at room temperature.

According to a further preferred process a) or b) compounds of general formula (III) and (IV) or

(V) are added to boiling 50 percent aqueous ethanol, after 3 to 5 minutes the reaction mixture is acidified with a strong mineral acid, preferably with hydrochloric acid, then boiling is continued for further 13 to 15 minutes, and the mixture is poured over ice.

After concluded reaction the product is isolated, purified, if necessary, by column chromatography and, if desired, converted into an acid addition salt.

The starting materials, the hydrazino compounds of general formula (III), can be prepared by the process of Hungarian Patent No. 178,396.

The starting materials of general formula (IV) are known from the literature and can be prepared by known methods [Archiv der Pharmazie 295 (8), 627 to 639 (1962)].

The starting materials of general Formula (V) are also known from the literature and can be prepared by known methods [Acta Chim. Scand. 17, 1801 (1963)].

Moreover according to the invention pharmaceutical compositions which contain one or more compound(s) according to the invention as [an] active ingredient(s), suitably together with one or more pharmaceutical carrier(s) and/or excipient(s), are provided for.

These pharmaceutical compositions advantageously may be in the form of tablets, capsules or solutions.

Furthermore advantageously they may be in a form suitable for oral or parenteral administration.

The pharmaceutical compositions according to the invention may be prepared in a manner known per se by admixing one or more compound(s) according to the invention with one or more pharmaceutical carrier(s) and/or excipient(s).

The compounds of the invention possess valuable biological properties, they are potent $PGF_{2alpha}$ receptor antagonists. In vitro, in the isolated rat uterus (Table 1), and in vivo in rabbits under urethane anesthesis (Table 2) they antagonize the uterine contraction inducing activity of $PGF_{2alpha}$. The competitive antagonist effect of the compounds is selective and protracted, while it fails to influence the uterine contraction inducing effect of other endogeneous compounds, i.e. oxytocin. This enables their use as spasmolytic agents of new mechanism of action in the field of obstetrics and gynecology for the treatment of dysmenorrhea and anovulation, and the prevention of imminent and habitual abortus and miscarriage.

In addition to the antiprostaglandin effect the compounds of the invention possess further pharmacological properties, namely antiserotonine, hypotensive, prolactine-level reducing, and significant dopamine receptor agonist effect, which may be exploited for the therapy of various conditions, such as bronchial asthma and disturbances in gastrointestinal motility.

The advantageous therapeutical properties of the compounds are accompanied by low toxicity (Table 3). The human dose amounts to 0.5 to 3 mg/kg body weight daily.

Table 1

$PGF_{2alpha}$ antagonist effect of the compounds of general formula (I) in vitro in isolated rat uterus

Method: 1. J.H. Gaddum and K.A. Hammed: Brit. J. Pharmacol. 9, 240 (1954)

2. O. Arunlakshana and H.O Schild: Brit. J. Pharmacol. 14, 48-58 (1959)

| Compound (Example No.) | Percentual inhibition at concentrations of $2x10^{-6}$ M against $1.4x10^{7}$ M $PGF_{2alpha}$ |
|---|---|
| 1 | 70 |
| 2 | 58 |
| 5 | 46 |
| 9 | 40 |
| 10 | 66 |
| 11 | 80 |
| 14 | 77 |
| 15 | 40 |

| Compound (Example No.) | Percentual inhibition at concentrations of $2x10^{-6}$ M against $1.4x10^{7}$ M $PGF_{2alpha}$ |
|---|---|
| 16 | 18 |
| 17 | 44 |

Table 2

In vivo $PGF_{2alpha}$ antagonist effect of pyrazole derivatives of general formula (I) in urethane (1.2 g/kg iv) anesthesized rabbits

Method: 1. D.F. Hawkins: Agents Acting on the Uterus. In: Evaluation of Drug Activities: Pharmacometrics. Edited by R. Lawrence and A.L. Bacharach. Academic Press, London, p. 680 (1964)

2. A.R. Cushny: J. Physiol. 35, 1 (1906)

| Compound (Example No.) | No. of animals n | Dose mg/kg intra-duodenal | Inhibition % | Duration of the effect minute |
|---|---|---|---|---|
| 1 | 12 | 0.3 | 38 | >180 |
| | 5 | 1.0 | 49 | >180 |
| Hydrogen-fumarate of 1 | 12 | 3.0 | 63 | >180 |

| Compound (Example No.) | No. of animals n | Dose mg/kg intra-duodenal | Inhibition % | Duration of the effect minute |
|---|---|---|---|---|
| 9 | 7 | 3.0 | 58 | >180 |
| | 9 | 10.0 | 68 | >180 |
| 17 | 6 | 10.0 | 55 | 120 |
| | 6 | 20.0 | 77 | >150 |
| 10 | 3 | 20.0 | 42 | 90 |
| 11 | 3 | 20.0 | 72 | >120 |

$PGF_{2alpha}$ standard dose: 6.25 µg/kg iv

Table 3

Acute toxicity of pyrazole derivatives of general formula (I) in CFLP mice

Method: Probite analysis according to Litchfield--Wilcoxon [J. Pharm. Exp. Ther. 96, 99 (1949)]

| Compound (Example No.) | $LD_{50}$ mg/kg ip | $LD_{50}$ mg/kg po | No. of animals n |
|---|---|---|---|
| 1 | 3100 | 2450 | 10 |
| 2 | >100 | >100 | |
| 4 | >100 | >100 | |
| 5 | >100 | >100 | |

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Table 3

contd.

| Compound (Example No.) | $LD_{50}$ mg/kg ip | po | No. of animals n |
|---|---|---|---|
| 6 | >200 | 1000 | |
| 7 | >100 | >100 | |
| 8 | >100 | >100 | |
| 9 | >100 | >100 | |
| 10 | >100 | >100 | |
| 11 | >100 | >100 | |
| 14 | >100 | >100 | |
| 15 | >100 | >100 | |
| 16 | >100 | >100 | |
| 17 | >100 | >100 | |
| 18 | >100 | >100 | |

The following examples are illustrative of the invention.

Example 1

8-beta-[3(6)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

{8-beta-[3(5)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene}

5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene are dissolved at room temperature under vigorous stirring in 100 ml of 50 percent aqueous ethanol, then 3.0 g (0.024 M) of 2-acetyl-cyclopentanone are added, and the mixture is acidified with 1 N aqueous hydrochloric acid to pH 3 to 4. The mixture is stirred at room temperature in the dark for one hour, then its pH is adjusted to pH 9 with a concentrated ammonium hydroxide solution, thereafter it is diluted with 200 ml of water and is extracted three times with 100 ml of dichloromethane. The combined organic layers are dried over sodium sulfate and are subsequently evaporated to dryness at reduced pressure. The reaction product is purified by column chromatography. The crude product is dissolved in the eluting solvent and layered over a column prepared from 200 g of silicagel. Elution is carried out with a 100:0.17:3.7 (volume ratio) mixture of chloroform-water-methanol, and the purity of the compound is controlled by thin-layer chromatography on 0.25 mm silicagel plates (adsorbent Kieselgel G nach Stahl). Length of development 20 cm, visualization with van Urk reagent (E. Stahl: Dünnschichtchromatographie. Springer Verlag 1967, p. 825). The eluates are evaporated to dryness at reduced pressure and the residue is recrystallized from 150 ml of 96 percent ethanol, yielding colourless needles of 4 g. Further 1 g of the

product can be recovered from the mother liquor. Yield: 70 percent.
Mp.: 214 to 215 °C, $[\alpha]_D^{20} = +90.3°$ (c = 0.2, ethanol).

Hydrogen fumarate salt:

1.25 g (0.0035 M) of 8-beta-[3(5)-methyl-cyclopentano/4,5(3,4)/pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene are dissolved in 70 ml of warm isopropanol, then 0.402 g (0.0035 M) of fumaric acid, dissolved in a mixture of 16 ml of isopropanol and 0.5 ml of water, is added to the hot solution. The hot solution is filtered, evaporated at reduced pressure to half of its volume, then the wall of the flask is scratched till the onset of crystallization, and the mixture is left to stand in the dark overnight at 0 to 5 °C, yielding 1.30 g of crystalline 8-beta-[3(5)-methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene hydrogen fumarate. M.p.: 181 to 183 °C (decomposition), $[\alpha]_D^{20} = +81.5°$ (c = 0.2, ethanol). Further 0.25 g portion of the product can be obtained by concentrating the mother liquor. Yield: 94 percent.

Example 2

8-beta-[3(6)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-1,6-dimethyl-ergol-9-ene hydrogen maleinate

{8-beta-[3(5)-Methyl-cyclopentano/4,5(3.4)/-
-pyrazol-1-yl-methylene]-1,6-dimethyl-ergol-
-9-ene hydrogen maleinate}

Sodium-amide is prepared from 0.29 g (0.0126 gatom) of metal sodium in 250 ml of anhydrous liquid ammonia, then 1.79 g (0.005 M) of 8-beta-[3(5)-methyl-cyclopentano/4,5(3,4)]pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene, dissolved in 20 ml of anhydrous tetrahydrofuran, are added. After 10 minutes the mixture is cooled to -50 °C, and dropwise 2.5 g (0.018 M) of methyl-iodide in 10 ml of anhydrous ether are added. Then the reaction mixture is left to warm up to the boiling point of liquid ammonia, and it is stirred there for a further 30 minutes. The progress of the reaction is monitored by thin-layer chromatography. At concluded reaction 10 ml of ethanol are added dropwise to the mixture and the ammonia is evaporated. The residue is taken up in dichloromethane, washed with water, then it is evaporated at reduced pressure. The residue is dissolved in 20 ml of ethanol and is treated in boiling solution with charcoal, then it is filtered. Subsequently a solution of 0.58 g of maleic acid, in a mixture of 10 ml of ethanol and 0.1 ml of water, is added dropwise to the filtrate. Then the solution is evaporated to half of its volume at reduced pressure. During several days of standing in the cool white

crystals are formed. Yield: 0.55 g (22.5 percent). M.p.: 160 °C (decomposition), $[\alpha]_D^{20} = +69.7^\circ$ (c = 0.2, ethanol).

Example 3

8-beta-[Cyclopentano/3,4(4,5)/pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 2.57 g (0.023 M) of 2-formyl-cyclopentanone the procedure described in Example 1 is applied. Yield: 2.76 g (40 percent) of a crystalline product. M.p.: 235 to 237 °C, $[\alpha]_D^{20} = +90.1^\circ$ (c = 0.2, ethanol).

Example 4

8-beta-[3(6)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergoline

{8-beta-[3(5)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergoline}

Starting from 5.41 g (0.02 M) of 8-beta-hydrazino-methyl-ergoline and 3 g (0.024 M) of 2-acetyl-cyclopentanone the procedure described in Example 1 is applied. Yield: 4.9 g (68 percent) of a white, crystalline product. M.p.: 188 to 190 °C, $[\alpha]_D^{20} = +101.2^\circ$ (c = 0.2, tetrahydrofuran).

 

Example 5

8-beta-[3(6)-(3-Pyridyl)-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

{8-beta-[3(5)-(3-Pyridyl)-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene}

5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene are dissolved in 150 ml of anhydrous methanol at room temperature, then a solution of 4 g (0.021 M) of 2-nicotinoyl-cyclopentanone in 20 ml of methanol is added, and subsequently at ice cooling 3.3 ml (0.024 M) of boron trifluoride - acetic acid complex solution (boron trifluoride content 36 percent) are added dropwise. Cooling is discontinued and the mixture is stirred for one hour at room temperature. Then the mixture is poured over a mixture of 100 g of crushed ice and 400 ml of water, it is made alkaline with a solution of ammonium hydroxide to pH = 9, and it is extracted four times with 80 ml of dichloro-methane. The combined organic layers, washed with water, are dried over sodium sulfate, and evaporated to dryness at reduced pressure. The residue obtained is purified by column chromatography according to the procedure described in Example 1. Yield: 3.5 g of a pale yellow, crystalline product. Recrystallized from methanol, m.p.: 140 to 141 °C, $[\alpha]_D^{20} = +86.3°$ (c = 0.2, ethanol). Yield: 42 percent.

Preparation of the starting 2-nicotinoyl--cyclopentanone

Starting from 15.3 g (0.10 M) of 1-morpholino--cyclopentene and 16.6 g (0.11 M) of nicotinoyl-chloride the procedure described by Eistert is followed [Berichte 94, 2591 (1961)], yielding 9.5 g of the product (50.2 percent) as a pale yellow oil solidifying at room temperature. B.p.: 152 to 154 °C/133 Pa.

Example 6

8-beta-[3(6)-Methyl-4(5)-oxo-cyclopentano-/4,5(3,4)/pyrazol-1-yl-methylene]-6-methyl--ergol-9-ene

2.68 g (0.01 M) of 6-methyl-8-beta-hydrazino--methyl-ergol-9-ene and 1.80 g (0.013 M) of 2-acetyl--cyclopenta-1,3-dione are simultaneously added at vigorous stirring to 150 ml of boiling, preferably 50 percent aqueous, ethanol. After 4 minutes 15 ml of 2 N aqueous hydrochloric acid are added in one portion to the reaction mixture which is refluxed for additional 15 minutes. Then it is poured over 200 g of crushed ice, adjusted with ammonium hydroxide to pH = 9 and extracted five times with 80 ml of dichloromethane. The combined extracts are dried over sodium-sulfate, then they are evaporated to dryness at reduced pressure and the residue is purified by column chromatography, using a column prepared from

100 g of silicagel, dissolved in the eluting solvent. Elution is carried out with a 100:0.2:5 (volume ratio) mixture of chloroform, water and methanol. Evaporating the eluates at reduced pressure yields 2.3 g of white crystals. Yield: 62 percent. After repeated crystallization from ethanol m.p.: 216 to 218 °C, $[\alpha]_D^{20} = + 100.6^\circ$ (c = 0.2, chloroform).

Example 7

8-beta-[3(6)-Methyl-4(5)-hydroxy-cyclopentano-/4,5(3,4)/pyrazol-1-yl-methylene]-6-methyl--ergol-9-ene

A solution of 3.72 g (0.01 M) of 8-beta-[3(6)--methyl-4(5)-oxo-cyclopentano/4,5(3,4)/pyrazol-1-yl--methylene]-6-methyl-ergol-9-ene (Example 6) in 80 ml of anhydrous tetrahydrofuran is added within 10 minutes to a vigorously stirred suspension of 0.5 g (0.013 M) of lithium aluminium hydride in 200 ml of anhydrous tetrahydrofuran. The solution is refluxed at constant stirring for 20 minutes, then it is left to cool. The excess of lithium aluminium hydride is decomposed with water, 100 ml of ethanol are added, and the suspension is filtered. The filtered aluminum oxide is extracted with 100 ml of hot ethanol. The combined extracts and filtrate are evaporated to dryness at reduced pressure. 100 ml of water is added to the residue which is extracted

with a mixture of chloroform-isopropanol (volume ratio: 3:1) till the organic layer no longer gives a positive van Urk reaction. The combined organic extract is dried over sodium sulfate and evaporated to dryness at reduced pressure, yielding 3.0 g (80 percent) of white crystals. Repeated crystallization results in an m.p. of 226 to 228 °C (decomposition), $[\alpha]_D^{20} = +86.3^\circ$ (c = 0.2, ethanol).

Example 8

8-beta-[3(6)-Methyl-4(5)-hydroxy-imino-cyclopentano/4.5(3,4)/pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

1 g (0.0027 M) of 8-beta-[3(6)-methyl-4(5)-oxo-cyclopentano/4,5(3,4)/pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene (Example 6) is dissolved in 100 ml of 96 percent ethanol, 1.0 g (0.014 M) of hydroxylamine hydrochloride in 1 ml of water and 1.95 ml (0.014 M) of triethyl amine are added and the entire mixture is refluxed for 6 hours. Then the solution is evaporated to dryness at reduced pressure. 40 ml of water are added to the residue, which is then extracted with a 3:1 (volume ratio) mixture of chloroform and isopropanol till the organic layer no longer gives positive van Urk reaction. The combined organic layers are washed with water, dried over sodium sulfate and evaporated to dryness at reduced pressure,

yielding 1 g (96 percent) of a crystalline product. Recrystallized from ethanol, the m.p. is 260 °C, $[\alpha]_D^{20} = +81.3^\circ$ (c = 0.2, ethanol).

Example 9

8-beta-[3(7)-Methyl-cyclohexano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

{8-beta-[3(5)-Methyl-cyclohexano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene}

Starting from 5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 3.0 g (0.021 M) of 2-acetyl-cyclohexanone, the procedure described in Example 1 is applied, yielding 5.1 g (67 percent) of a white, crystalline product, m.p.: 173 to 175 °C, $[\alpha]_D^{20} = +68.3^\circ$ (c = 0.2, ethanol).

Example 10

8-beta-[(3(7),6(4),6(4)-Trimethyl-4(6)-oxo-cyclohexano/4,5(3,4)/pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 2.68 g (0.01 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 2.36 g (0.013 M) of 2-acetyl-5,5-dimethyl-cyclohexa-1,3-dione (2-acetyl-dimedone), the procedure described in Example 6 is

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applied. Chromatography is carried out with an eluting solvent of 100:0.1:3 (volume ratio) chloroform-water--methanol. Yield: 2.4 g (58 percent) of a white crystalline product. Recrystallized from ethanol m.p.: 200 °C. $[\alpha]_D^{20} = + 84.5°$ (c = 0.2, ethanol).

Example 11

8-beta-[3(7),6(4),6(4)-Trimethyl-4(6)-hydroxy--imino-cyclohexano/4,5(3,4)/pyrazol-1-yl--methylene]-6-methyl-ergol-9-ene

4.14 g (0.01 M) of 8-beta[3(7),6(4),6(4)-Trimethyl-4(6)-oxo-cyclohexano/4,5(3,4)/pyrazol-1-yl--methylene]-6-methyl-ergol-9-ene (Example 10) are dissolved in 250 ml of hot ethanol. At first 5.15 g (0.10 M) of hydroxylamine hydrochloride and then 13.9 ml (0.10 M) of triethylamine are added, and the entire mixture is refluxed for 30 hours. The progress of the reaction is monitored by thin-layer chromatography. The developing solvent is a 100:22:1.7 (volume ratio) mixture of chloroform, methanol and water, while the visualizing reagent is van Urk's. When the starting material disappears from the solution, the ethanol is evaporated at reduced pressure, 80 ml of water are added to the residue, its pH is adjusted to pH = 9 with a solution of ammonium hydroxide, then the solution is extracted with a 3:1 (volume ratio) mixture of chloroform and isopropanol till a drop of the organic phase fails to give a positive van Urk re-

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action. The combined organic phases are dried over sodium sulfate and subsequently evaporated to dryness at reduced pressure. The evaporation residue is dissolved in hot ethanol, decolourized with charcoal, and it is concentrated to one third of its volume. The crystals formed from the concentrated solution are filtered and dried. Yield: 3.87 g (90 percent). M. p.: 230 °C (decomposition).

Example 12

8-beta-[3,5-Dimethyl-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 2.2 g (0.022 M) of pentane-2,4-dione, the procedure described in Example 1 is applied, except that instead of submitting to chromatography the evaporation residue of the dichloromethane solution, it is dissolved in 250 ml of hot ethanol and decolourized with charcoal. The crystals formed at the cooling of the solution are filtered and combined with the second crop of crystals obtained by the concentration of the mother liquor. Yield 4.64 g (70 percent) of a white, crystalline product. M. p.: 218 to 220 °C, $[x]_D^{20} = + 72.1^{\circ}$ (c = 0.2, ethanol).

Example 13

8-beta-(3,5-Dimethyl-4-ethyl-pyrazol-1-yl--methylene)-6-methyl-ergol-9-ene

Starting from 5.37 g (0.02 M) of 6-methyl-8--beta-hydrazino-methyl-ergol-9-ene and 3 g (0.023 M) of 3-ethyl-pentane-2,4-dione, the procedure described in Example 1 is applied. Yield: 4.5 g (62 percent) of a white, crystalline product. M. p.: 175 to 177 °C, $[\alpha]_D^{20} = +61.5°$ (c = 0.2, ethanol).

Example 14

8-beta-(3,5-Dimethyl-4-allyl-pyrazol-1-yl--methylene)-6-methyl-ergol-9-ene

Starting from 5.37 g (0.02 M) of 6-methyl-8--beta-hydrazino-methyl-ergoline or 6-methyl-8--beta-hydrazino-methyl-ergol-9-ene and 3.4 g (0.024 M) of 3-allyl-pentane-2,4-dione, the procedure described in Example 1 is applied. Yield: 4.5 g (60 percent) of a white, crystalline product. M. p.: 177 to 178 °C, $[\alpha]_D^{20} = +63.5°$ (c = 0.2, ethanol).

Example 15

8-beta-(3-Carbethoxy-4-methyl-5-hydroxy--pyrazol-1-yl-methylene)-6-methyl-ergol-9-ene

Starting from 5.37 g (0.02 M) of 6-methyl-8--beta-hydrazino-methyl-ergol-9-ene and 4.85 g (0.024 M)

of 2-oxalyl-propionic acid diethyl ester, the procedure described in Example 1 is applied. Yield: 4.87 g of a white, crystalline product. M. p.: 150 to 151 °C, $[\alpha]_D^{20}$ = + 39.5° (c = 0.2, ethanol).

Example 16

8-beta-[3(5)-/2-Pyridyl/-5(3)-methyl-pyrazol-1--yl-methylene]-6-methyl-ergol-9-ene

With 5.37 g (0.02 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 3.9 g (0.024 M) of (2-pyridyl)-butane-1,3-dione the procedure described in Example 5 is applied. Yield: 4.0 g (50.6 percent) of a white crystalline product. M. p.: 226 to 228 °C, $[\alpha]_D^{20}$ = = +73.5° (c = 0.2, ethanol).

Example 17

8-beta-[3(5)-/2-Pyridyl/-5(3)-methyl-pyrazol-1--yl-methylene]-6-methyl-ergoline

Starting from 5.41 g (0.02 M) of 6-methyl-8--beta-hydrazino-methyl-ergoline {6-methyl-8--beta-hydrazino-methyl-ergol-9-ene} and 3.9 g (0.024 M) of (2-pyridyl)-butane-1,3-dione the procedure described in Example 5 is applied. Yield: 4.3 g (54 percent). Recrystallized from a mixture of dichloroethane and chloroform m. p. 265 to 267 °C.

Example 18

8-beta-[3,5-Dimethyl-4-(1-oxo-ethyl)-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 2.68 g (0.01 M) of 6-methyl-8-beta-hydrazino-methyl-ergol-9-ene and 2.80 g (0.02 M) of triacetyl-methane the procedure described in Example 6 was applied. Recrystallization from ethanol yielded 1.42 g (38 percent) of the product. M. p.: 228 to 232 °C, $[\alpha]_D^{20} = + 78.6^\circ$ (c = 0.2, chloroform). During chromatography 0.07 g of 8-beta-(3,5-dimethyl-pyrazol-1-yl-methylene)-6-methyl-ergol-9-ene can be obtained from the last fractions as a by-product. M. p.: 218 to 220 °C, $[\alpha]_D^{20} = + 72.1^\circ$ (c = 0.2, ethanol). Mixed with the former product it gives significant m. p. depression.

Example 19

8-beta-[3,5-Dimethyl-4-(1-hydroxy-ethyl)-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 3.75 g (0.01 M) of 8-beta-[3,5-dimethyl-4-(1-oxo-ethyl)-pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene (Example 18) and 0.5 g (0.013 M) of lithium aluminium hydride the procedure described in Example 7 is applied, yielding 2.71 g (72 per cent) of the product. Recrystallized repeatedly from ethanol m. p.: 212 to 214 °C, $[\alpha]_D^{20} = + 40.1^\circ$ (c = 0.2, chloroform).

Example 20

8-beta-[3,5-Dimethyl-4-(1-hydroxy-imino-ethyl)--pyrazol-1-yl-methylene]-6-methyl-ergol-9-ene

Starting from 3.75 g (0.01 M) of 8-beta-[3,5--dimethyl-4-(1-oxo-ethyl)-pyrazol-1-yl-methylene]-6--methyl-ergol-9-ene (Example 18), 3.48 g (0.05 M) of hydroxylamine hydrochloride and 7 ml (0.05 M) of triethyl amine the procedure described in Example 8 is applied, yielding 3.72 g (90 per cent) of the product. Recrystallized from 96 percent ethanol m. p. higher than 260 °C. $[\alpha]_D^{20} = +37.9^\circ$ (c = 0.2, 96 percent ethanol).

Example 21

Pharmaceutical composition

Composition of one tablet:

| | |
|---|---|
| 8-beta-[3(5)-Methyl-cyclopentano/4,5(3,4)/-pyrazol-1-yl-methylene]-6-methyl-ergol--9-ene hydrogene fumarate | 50.0 mg |

| | |
|---|---|
| Avicel PH 102® * (microcrystalline cellulose) | 46.5 mg |
| Aerosil-200® ** (colloidal $SiO_2$) | 0.5 mg |
| Stearic acid (powder) | 2.5 mg |
| Magnesium stearate | 0.5 mg |
| | 100.0 mg |

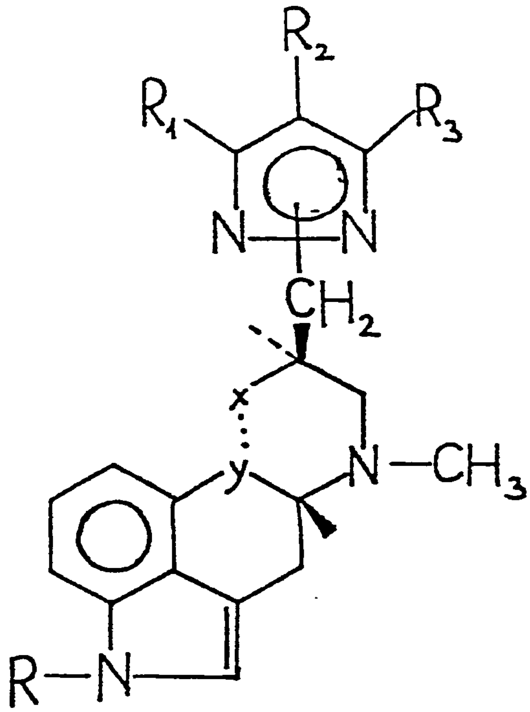
* FMC Corporation (Pennsylvania USA)

** Degussa (FRG)

Claims

## Claims

1.) Pyrazole derivatives with an ergoline skeleton of general formula



I ,

wherein

x...y stands for a group of formula

$$\underset{}{-\overset{\text{H}}{\overset{|}{\text{C}}}=\underset{|}{\text{C}}-} \quad \text{or} \quad -\underset{\text{H}_2}{\text{C}}-\underset{|}{\overset{\text{H}}{\overset{|}{\text{C}}}}- \quad ,$$

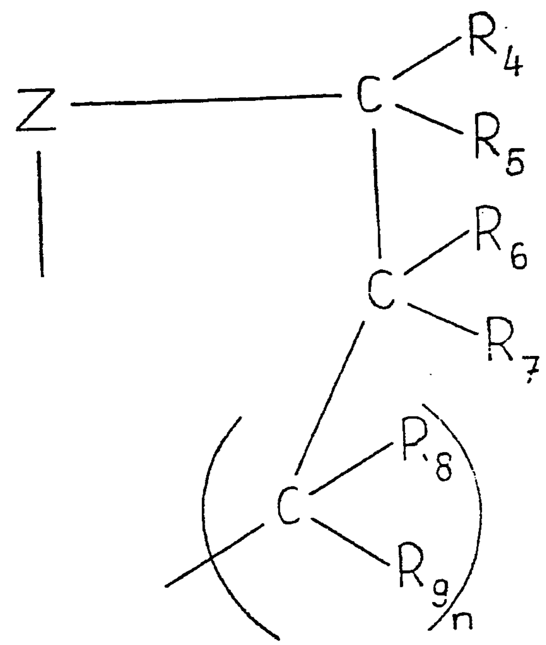
R means a hydrogen atom or a methyl group,

$R_1$ represents a hydrogen atom or a $C_{1-4}$-alkyl, carbethoxy or pyridyl group and either

$R_2$ stands for a hydrogen atom or a $C_{1-4}$--alkyl, allyl, $C_{2-4}$-oxoalkyl, $C_{2-4}$--hydroxyalkyl or $C_{2-4}$-hydroxyimino-alkyl group and

$R_3$ means a hydrogen atom or a $C_{1-4}$-alkyl, hydroxy or pyridyl group or

$R_2$ and $R_3$ together stand for a group of general formula



II ,

in which latter

Z stands for a methylene group, optionally substituted by one or two $C_{1-4}$-alkyl group(s), or a carbonyl, hydroxymethylene or hydroxyiminomethylene group,

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$R_4$ , $R_5$ ,
$R_6$ , $R_7$ ,
$R_8$ and
$R_9$ ; independently from each other, mean hydrogen atoms or $C_{1-4}$-alkyl groups and

n is 0 or 1,

as well as their pharmaceutically acceptable salts.

2.) Pyrazole derivatives according to claim 1, characterized in that the $C_{1-4}$-alkyl group(s) which may be represented by $R_1$ , $R_2$ , $R_3$ , $R_4$ , $R_5$ , $R_6$ , $R_7$ , $R_8$ and/or $R_9$ is or are such having 1 or 2, particularly 1, carbon atom(s).

3.) Pyrazole derivatives according to claim 1 or 2, characterized in that the $C_{2-4}$-oxoalkyl, $C_{2-4}$-hydroxyalkyl or $C_{2-4}$-hydroxyiminoalkyl group which may be represented by $R_2$ is such having 2 or 3, particularly 2, carbon atoms.

4.) Pyrazole derivatives according to claims 1 to 3, characterized in that the $C_{1-4}$-alkyl group(s) by which the methylene group for which Z may stand may be substituted is or are such having 1 or 2, particularly 1, carbon atom(s).

5.) Pyrazole derivatives according to claims 1 to 4, characterized in that formula II has from 1 to 3 $C_{1-4}$-alkyl group(s) as [a] substituent(s).

6.) 8-ß-{3(5)-Methyl-cyclopentano[4,5(3,4)]pyrazol-1-yl-methylene}-6-methyl-ergol-9-ene.

7.) 8-ß-{3(5)-Methyl-cyclopentano[4,5(3,4)]pyrazol-1-yl-methylene}-6-methyl-ergol-9-ene hydrogen-fumarate.

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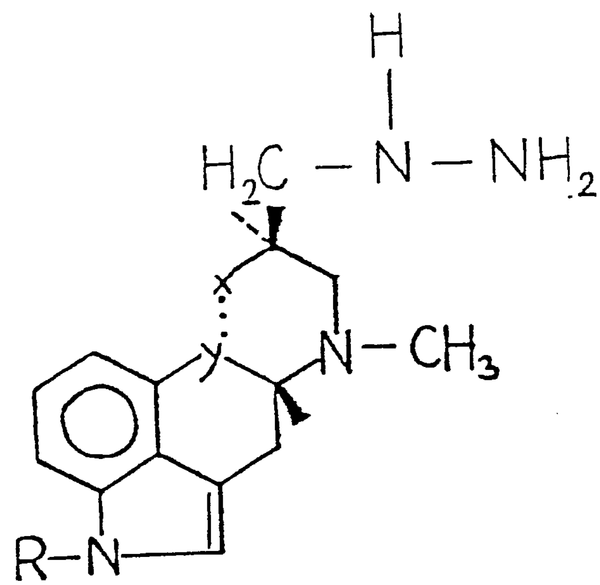
8.) A process for preparing the compounds according to claims 1 to 7, characterized in that hydrazine compounds of general formula

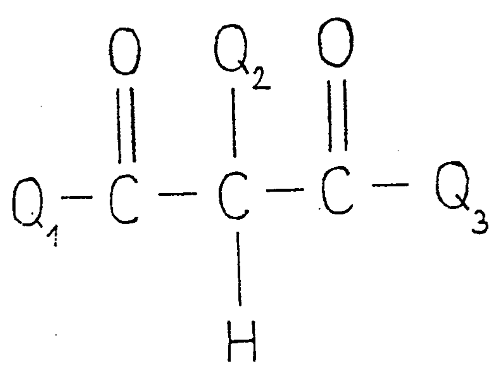


III ,

wherein x...y and R are as defined in claim 1,

are reacted

a) with ß-diketones of general formula



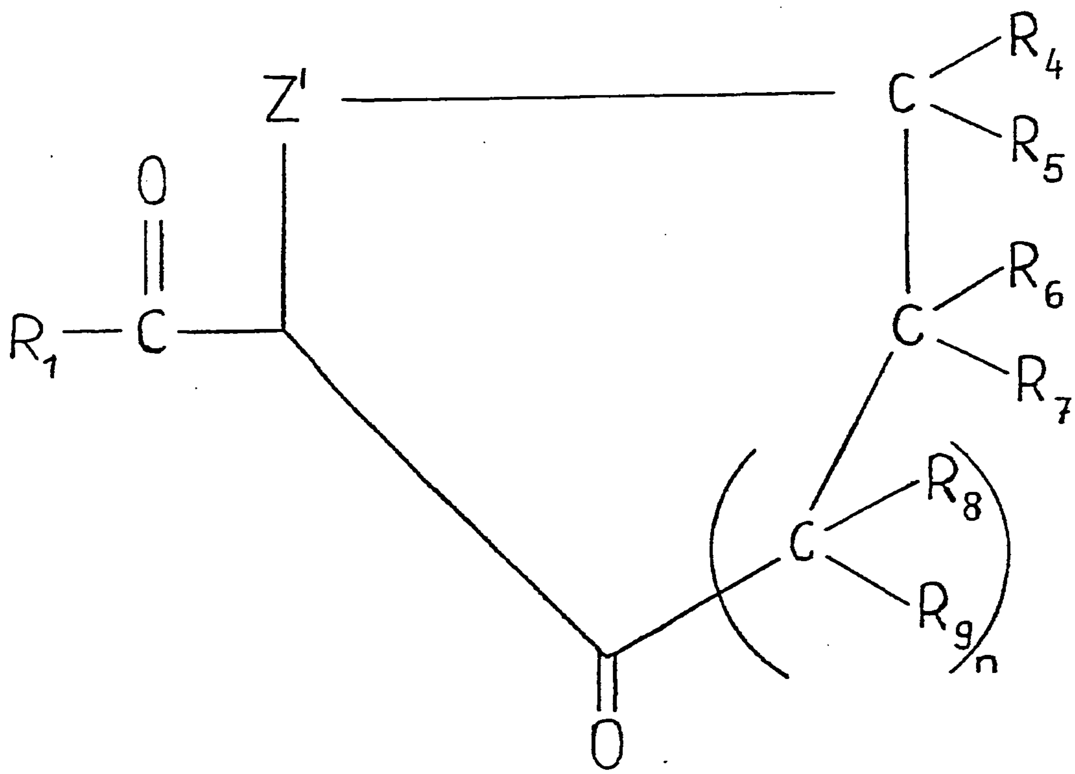
IV ,

wherein

$Q_1$ and $Q_3$ , independently from each other, stand for a $C_{1-4}$-alkyl, ethoxy, carbethoxy or pyridyl group and

$Q_2$ represents a hydrogen atom or a $C_{1-4}$-alkyl, allyl or $C_{2-4}$-oxoalkyl group or

b) with cycloalkanones of general formula



V ,

wherein

$R_1$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$ and n are as defined in claim 1 or 2 and

Z' stands for a methylene group, optionally substituted by one or two $C_{1-4}$-alkyl group(s), or for a carbonyl group,

whereafter, if desired, in a manner known per se the obtained pyrazole derivatives of general formula I in which x...y stands for a group of formula $-\overset{H}{\overset{|}{C}}=\underset{|}{C}-$ and/or $R_2$ represents a $C_{2-4}$-oxoalkyl group or Z represents a carbonyl group are reduced to those in which x...y stands for a group of formula $-\underset{H_2}{C}-\overset{H}{\underset{|}{\overset{|}{C}}}-$ and/or $R_2$ represents a $C_{2-4}$-hydroxyalkyl group or Z represents a hydroxymethylene group, respectively, or, if desired, the obtained pyrazole derivatives of general formula I in which $R_2$ represents a $C_{2-4}$-oxoalkyl group or Z represents a carbonyl group are converted into the corresponding pyrazole derivatives of general formula I being oximes in which $R_2$ represents a $C_{2-4}$-hydroxy-iminoalkyl group or Z represents a hydroxyiminomethylene group, respectively, or, if desired, the obtained pyrazole derivatives of general formula I in which R stands for a hydrogen atom are methylated to the corresponding pyrazole derivatives of general formula I in which R stands for a methyl group and/or, if desired, the whatever obtained pyrazole derivatives of general formula I are converted with acids into salts or, if desired, the whatever obtained salts of the pyrazole derivatives of general formula I are converted into the corresponding free bases of general formula I and/or into other salts.

9.) Pharmaceutical compositions characterized by a content of one or more compound(s) according to claims 1 to 7 as [an] active ingredient(s), suitably together with one or more pharmaceutical carrier(s) and/or excipient(s).

Abstract